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Serial No.: 09/738,599

Confirmation No.: 1240

Filed: 15 December 2000

For: NUCLEIC ACID ENCODING AN AVIAN E. COLI ISS POLYPEPTIDE & METHODS OF USE**Remarks**

The Office Action mailed 10 August 2005 has been received and reviewed. Claims 70, 71, and 73 having been amended, the pending claims are claims 30-33, 35-42, and 44-73, with claims 30-33, 37-42, 44, 45, and 67-73 being currently under examination. Reconsideration and withdrawal of the rejections are respectfully requested.

Allowed Claims

Applicants thank the Examiner for notification that claims 30-33 and 69 contain allowable subject matter.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner maintained the rejection of claim 70 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner also maintained the rejection of claim 70 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These rejections are respectfully traversed. However, Applicant has amended the claim to conform to the phrasing regarding the immunogenic fragments used in claims 37 and 68, as helpfully suggested by the Examiner.

The Examiner rejected claims 71-73 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner alleged that there is no descriptive support in the

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specification at page 28-29, lines 1-4 for such product comprising the specifically recited nucleotide sequences and a eukaryotic promoter wherein the recited polypeptide, or immunogenic fragment or immunogenic subunit thereof is expressed in an animal cell, or wherein the eukaryotic promoter and the nucleic acid molecule forms an expression vector suitable for use in an animal cell, as recited. This rejection is respectfully traversed.

"The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." M.P.E.P. §2163(I)(B). "While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure." M.P.E.P. §2163(I)(B).

The Examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims (M.P.E.P. §2163(III)(A)), and it is respectfully submitted that the Examiner has not met this burden. The Examiner has not provided reasons that amount to a preponderance of evidence as to why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. Thus, the Examiner has not established a *prima facie* case. The only reason offered by the Examiner for the lack of adequate written description is that "there is no descriptive support in the instant application for such a product comprising the specifically recited nucleotide sequences and a eukaryotic promoter wherein the recited polypeptide, or immunogenic fragment or immunogenic subunit thereof is expressed in an animal cell, or wherein the eukaryotic promoter and the nucleic acid molecule forms an expression vector suitable for use in an animal cell, as recited." The Examiner is requested to consider the disclosures of the specification at, for instance, page 47, line 1 through page 48, line 17, and Example 5. In view of these disclosures, the Examiner's statement that "there is no descriptive support in the instant application for such a product" does not establish a preponderance of the evidence.

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The Examiner is respectfully requested to withdraw the rejection of claims 71-73 under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §112, Second Paragraph, Rejection

The Examiner rejected claims 71 and 73 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner alleged that claims 71 and 73 were vague and confusing in the limitation: 'an immunogenic fragment or immunogenic subunit thereof', because it is unclear whether the recited 'immunogenic fragment or immunogenic subunit thereof' is a subunit or fragment of 'the polypeptide', or of the 'avian *E. coli* Iss polypeptide'. Further, the Examiner alleged that claim 73 is vague, indefinite, and lacks antecedent basis in the limitation: 'an avian *E. coli* Iss polypeptide or an immunogenic fragment or immunogenic subunit thereof'. This rejection is respectfully traversed. However, Applicant has amended the claim to conform to the phrasing regarding the immunogenic fragments used in claims 37 and 68, as helpfully suggested by the Examiner.

The 35 U.S.C. §103 Rejection

The Examiner rejected claims 37-40, 67 and 68 under 35 U.S.C. §103(a) as being unpatentable over Bardonn *et al.* (*Nature* 344: 871-874, 1990) in view of Harlow *et al.* (In: *Antibodies: a Laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, page 76, 1988). This rejection is respectfully traversed.

The burden is on the Office to establish a *prima facie* case of obviousness of the claimed invention, and it is respectfully submitted that the Office has not met this burden. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

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M.P.E.P. §2143.

Barondess *et al.* (1990) disclose accessory sequences expressed during lysogeny, one of which was designated "*bor*." Barondess *et al.* notes that "*bor* and its adjacent sequences are highly homologous to the *iss* serum resistance locus of the plasmid ColV2-K94." Barondess' findings were of interest because they demonstrated how lysogeny contributed to bacterial virulence.

Barondess *et al.* do not teach all of the claim limitations of claims 37 and 68. More specifically, Barondess *et al.* do not teach or suggest a nucleotide sequence encoding a polypeptide comprising an avian *E. coli* *iss* polypeptide or an immunogenic fragment or immunogenic subunit of the avian *E. coli* *iss* polypeptide.

In addition to not teaching *iss* polypeptide from avian *E. coli*, there is no teaching or suggestion to modify the teachings of Barondess *et al.* as asserted by the Examiner. The Examiner asserts that the motivation comes from "the expected benefit of providing Barondess' (1990) nucleic acid as an immunogenic composition." Action at page 7. The statement made by the Examiner at page 7 of the Action may show that Barondess *et al.* could be modified; however, it does not provide any convincing line of reasoning as to why a skilled person would modify the document. For instance, no convincing line of reasoning is provided regarding why the skilled person would want to have an immune response to the Barondess *et al.* product, and even if they did, why they would do so by providing a nucleic acid as an immunogenic composition. The Examiner attempts to bolster the asserted motivation by stating "it is conventional in the art to add an art-known carrier to an art-known nucleic acid to facilitate its use for diagnostic or pharmaceutical purposes." However, convention is not a proper criterion for resolving the issue of obviousness. Further, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP § 2143.01.

Furthermore, Barondess *et al.* were investigating bacterial virulence, and in particular, how lysogeny by phage λ and the resultant transfer of virulence factors increase bacterial survival in animal hosts. Stimulating an immune response, on the other hand, generally has

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exactly the opposite effect; namely, it decreases bacterial survival. Thus, Barondess *et al.* teaches away from stimulating an immune response. Mere presentation of a deduced amino acid sequence cannot, by itself, be sufficient in every case to suggest preparation of an immunogenic composition as claimed in claims 37 and 68. The likelihood that Barondess *et al.* would teach or suggest the claimed immunogenic compositions is further decreased by the fact that Barondess *et al.* were not even investigating the antigen characteristics of *E. coli*, but rather were investigating the ability of lysogeny of phage λ to increase the survival of some *E. coli* strains in serum.

For at least the reasons provided above, Applicants assert that claims 37-40, 67 and 68 are not obvious under 35 U.S.C. §103(a), and respectfully request that the rejection of these claims be withdrawn.

The Examiner rejected claim 41 under 35 U.S.C. §103(a) as being unpatentable over Barondess *et al.* (*Nature* 344: 871-874, 1990) as applied to claim 37 above and further in view of Applicants' admitted state of the prior art. The Applicant notes this rejection is nearly identical to the rejection in the Office Action mailed July 30, 2004, at page 6. This rejection is respectfully traversed.

The Examiner asserts that "[o]ne of skill in the art would have been motivated to produce the instant invention for the expected benefit of improved expression of Barondess' polynucleotide since improved expression is ideally desired in the art." Action at page 8. It is respectfully submitted that a skilled person desiring improved expression of a nucleotide sequence normally expressed in *E. coli* would *not* be motivated to express the nucleotide sequence in an animal cell. At the time the present application was filed microbial cells, especially *E. coli*, were regarded as more desirable for protein expression than animal cells. For instance, microbial cells were known in the art as growing much faster than animal cells, requiring a much less complex and less expensive growth medium, and expressing higher levels of protein. If the skilled person were seeking improved expression of a nucleotide sequence normally expressed in *E. coli*, why would they express the sequence in animal cells? The Examiner has not provided a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious.

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The Examiner is requested to note that the present specification suggests that the skilled person could use animal cells for the expression of polypeptides; however, it does not state that the skilled person would be motivated to use an animal cell for expression of polypeptides. In this regard, the Examiner is requested to note that a "statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is *not sufficient* to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references." M.P.E.P. §2143.01 (emphasis added). The Examiner may have provided an objective reason, i.e., improved expression, but the skilled person that seeks improved expression of a bacteriophage gene would not be motivated to use animal cells.

"The tendency to resort to 'hindsight' based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." M.P.E.P. § 2142. The Examiner has not provided any reason why the skilled person would use an animal cell for improved expression of a bacteriophage gene, and has merely taken the applicant's disclosure and used it as a blueprint for putting together a rejection to defeat the patentability of the present invention.

The Examiner rejected claim 42 under 35 U.S.C. §103(a) as being unpatentable over Bardness *et al.* (Nature 344: 871-874, 1990) as applied to claim 38 above, and further in view of Krieg *et al.* (WO 96/02555). The Applicant notes this rejection is nearly identical to the rejection in the Office Action mailed July 30, 2004, at page 9. This rejection is respectfully traversed.

It is respectfully submitted that there is no motivation to combine Bardness *et al.* and Krieg *et al.* to arrive at the present invention. The Office asserts that "[o]ne of skill in the art would have been motivated to produce the instant invention for the expected benefit of further enhancing the immune response to Bardness' (1990) product" (Action, page 9).

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The statement made by the Office at page 9 of Action may show that the documents could be combined to have the Barondess et al. product together with Krieg's immunostimulatory sequence; however, it does not provide any convincing line of reasoning as to why a skilled person would combine the documents. For instance, no convincing line of reasoning is provided regarding why the skilled person would want to have an immune response to the Barondess *et al.* product.

It is respectfully submitted that this rejection is another example of the use of hindsight by the Examiner. The cited documents, viewed by themselves and not in retrospect, must suggest doing what applicant has done. In re Shaffer 108 USPQ 326, 329 (CCPA 1956). The cited documents do not suggest doing what the applicants have done. Applicants thus assert that claim 42 is not obvious and that the rejection of claim 42 under 35 U.S.C. § 103(a) should be withdrawn.

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It is respectfully submitted that the pending claims 30-33, 37-42, 44, 45, and 67-73 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.8:

The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to **Mail Stop Amendment**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 10th day of November, 2005, at 10:47 a.m. (Central Time).

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